REMARKS

The Advisory Action of May 27, 2009, in which the prior art rejections are withdrawn and the §112 enablement rejections are maintained, has been carefully reviewed. Claims 1-7, 9-21 and 28-30 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1-5, 10-16 and 28-30 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The examiner takes the position that the specification, while being enabling for a method for attenuating the virulence of a microbial pathogen from *S. aureus* or for inhibiting or reducing colonization by a microbial pathogen from *S. aureus* in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP, cGMP and 5'-GMP to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, does not reasonably provide enablement for any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization

by, the microbial pathogen. This rejection is respectfully traversed.

The claims are amended without prejudice to refer only to "bacterial" pathogen instead of any "microbial" pathogen. Accordingly, part of this rejection for the scope of any "microbial" pathogen should be obviated by this amendment. The executed 1.132 declaration of David Karaolis attached hereto addresses this rejection as it may relate to "bacterial" pathogens. In light of the evidence and statements from the 1.132 declaration attached hereto and the evidence from the 1.132 declaration submitted with the amendment of October 6, 2008, it is clear that Example 8 on page 80 of the present specification does indeed demonstrate positive results in a challenged mouse model, contrary to the examiner's assertion, and that post-filing *in vitro* and *in vivo* experimental results in a broad range of gram positive and gram negative bacterial pathogens confirmed the activity of c-di-GMP and other cyclic dinucleotides in inhibiting microbial colonization, virulence and infection for *Staphylcoccus aureus* in a mouse mastitis model. The bacterial pathogens used in the experiments span from gram-positive cocci, *Staphylcoccus aureus* and *Streptococcus pneumoniae* (from two different families) to gram negative enteric *Klebsiella pneumoniae* (from the Enterobacteriaceae family) to gram negative *Ehrlichia chaffeensis*

of the Rickettsiales family to gram negative *Brucella melitensis* (from the family Brucellaceae). One of skill in the art would certainly appreciate that these representative examples of pathogenic bacteria cover a wide spectrum of bacteria that even includes intracellular bacterial pathogens from the less common bacterial pathogen families of Rickettsiales and Brucellaceae and would therefore reasonably expect, based on the evidence of record, that the presently claimed method would be enabled for the extended genus of bacterial pathogens.

Furthermore, positive *in vitro* and *in vivo* experimental results, as discussed in the attached 1.132 declaration and the 1.132 declaration filed October 6, 2008, were obtained with several different cyclic dinucleotides, including c-di-GMP, TBDMS-c-di-GMP, c-GpAp, c-GpIp and c-GpsGp, thereby providing evidence for the function of cyclic dinucleotides that all share a common core structure of cyclic (head to tail) ribo- or deoxyribo-nucleotides (with ribose moiety and purine or pyrimidine base). One of skill in the art would certainly understand and appreciate from the teachings of the present specification at paragraphs [0044]-[0046] that c-di-GMP may act to inhibit biofilm formation/colonization/virulence in some bacteria or it may act in the opposite manner and induce or enhance biofilm formation/colonization/virulence in others.

Thus, specific cyclic dinucleotides may act as either agonists or antagonists of c-di-GMP, a property that can be rapidly and readily determined with only routine experimentation using biofilm formation/inhibition assays in microtiter plates, test tubes or flasks, as disclosed in paragraph [0045] and in the examples of the specification.

Applicant also notes that on page 8 of the Advisory Action of May 27, 2009, the examiner cited Bowie et al., *Science* 247:1306-1310 (1990), for teaching the problem of predicting protein structure from sequence data. This citation is irrelevant as the three dimensional structure of a protein macromolecule has nothing to do with small cyclic dinucleotides, which is more analogous to small organic molecules having a common core structure with only differences in the substituent groups.

Accordingly, the presently claimed invention is certainly enabled to one of skill in the art and reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 17-21 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The examiner takes the position that the specification, while being enabling for a method for inhibiting

Staphylococcus aureus (S. aureus) colonization and *S. aureus* biofilm formation or for reducing *S. aureus* colonization and pre-formed *S. aureus* microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of c-di-GMP or a cyclic dinucleotide to inhibit *S. aureus* colonization and *S. aureus* biofilm formation or to reduce microbial colonization and preformed biofilm on said solid surface, does not reasonably provide enablement for any method for inhibiting bacterial colonization and biofilm formation or for reducing colonization and pre-formed bacterial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of c-di-GMP or a cyclic dinucleotide to inhibit bacterial colonization and biofilm formation or to reduce bacterial colonization and pre-formed biofilm on said solid surface. This rejection is respectfully traversed.

The examiner states on page 10 of the Advisory Action of May 27, 2009, that "contrary to Applicant's assertion, Applicant has not provided a copy of Mano et al., *Chem. Med. Chem.* 2:1410-1413 (2007), as evidence that cyclic dinucleotides, c-di-GMP and c-dGpGp, inhibited biofilm formation of three types of bacterial pathogens important to infections in humans." To clarify the record, this statement is clearly incorrect as the USPTO electronic acknowledgement receipt shows that the Mano et

al. (2007) publication filed with the amendment on October 6, 2008, was indeed received by the USPTO and appears on PAIR in the Bibliographic Data as an NPL document of four pages in length with a mailroom date of October 6, 2008. Nevertheless, the Mano et al. publication is re-submitted as Exhibit 2 of the executed 1.132 declaration attached hereto.

As stated in the attached 1.132 declaration, this Mano et al. publication demonstrated that two cyclic dinucleotides, c-di-GMP and c-dGpGp, inhibited biofilm formation of three different types of bacteria, *Pseudomonas aeruginosa* (gram positive), *Vibrio parahaemolyticus* (gram negative), and *Staphylococcus aureus* (gram positive), on a polystyrene solid surface (see page 1410, second full paragraph in right column). Based on the findings in this Mano et al. publication, in which three different biofilm forming bacteria (both gram positive and gram negative bacteria, cocci and rod-shaped bacteria) were tested with two different cyclic dinucleotides, one of skill in the art would certainly recognize and understand that these three bacteria are sufficiently representative of the genus of biofilm forming bacteria to reasonably expect that these same results of inhibiting biofilm formation and colonization with cyclic dinucleotides can be extrapolated and extended to the genus of biofilm forming bacteria. There is no basis to doubt this in

view of the evidence in Manos et al., the teachings of the instant specification, and applicant's statements in the attached 1.132 declaration. Accordingly, one of skill in the art is indeed enabled for the scope of claims 17-21.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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